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Published
With international search report.

(54) Title: PROCESS FOR THE PREPARATION OF PAROXETINE HYDROCHLORIDE

(57) Abstract

Solid forms of paroxetine hydrochloride (crystalline as well as amorphous) are obtained by precipitation from a supercritical or near–critical fluid such as carbon dioxide. This procedure offers the advantage of a more easily controlled precipitation process than is obtained by previously known methods, and better control of surface morphology, porosity, particle size and distribution.

This procedure offers the advantage of a more easily controlled precipitation process than is obtained by previously known methods, and better control of surface morphology, porosity, particle size and distribution. These factors are important and affect, for example, the rate of dissolution and the performance of the material in secondary pharmaceutical manufacturing.

Paroxetine hydrochloride is prepared for supercritical fluid precipitation by forming a solution in a supercritical fluid such as supercritical carbon dioxide. Other supercritical fluids such as ethane, n-propane, n-butane, and nitrogen oxide, may also be used. Known solid forms of paroxetine hydrochloride form such solutions with some difficulty. Therefore the paroxetine hydrochloride is preferably first dissolved in an auxiliary solvent, for example ethanol, propan-2-ol, or isobutyl alcohol, compatible with the supercritical fluid, and the solution brought into contact with the supercritical fluid to form a suitable solution for precipitation. A suitable solution may be prepared from amorphous paroxetine hydrochloride or a crystalline anhydrate, hydrate, or solvate of paroxetine hydrochloride, or by dissolving the free base and hydrochloric acid in an aqueous, organic or mixed aqueous and organic solvent. Indeed it may be possible to bring the free base and hydrochloric acid together in the supercritical domain where they may react prior to precipitation of paroxetine hydrochloride.

In order to achieve successful precipitation of paroxetine hydrochloride from a supercritical fluid by a method that uses an auxiliary solvent, this solvent preferably has an affinity for the supercritical fluid so that both may be effectively removed in a single process. The preferred auxiliary solvents listed above are not ideal in this respect, at least when the supercritical fluid is carbon dioxide, so it may be advantageous to employ an additional entraining solvent to confer suitable properties on the auxiliary solvent. An example of a suitable entraining solvent for use with propan-2-ol and supercritical carbon dioxide is acetone.

The entraining solvent may be combined with the auxiliary solvent in a ratio from 1:5 to 20:1, preferably from 1:1 to 10:1, and most preferably from 3:1 to 7:1. The concentration of paroxetine hydrochloride in the auxiliary solvent may be from 0.5% to 25%, but is preferably in the range 1% to 10%, for example from 2.5% to 5%. The supercritical solution for precipitation is formed by combining the paroxetine hydrochloride solution with supercritical fluid in its liquid phase in a ratio of from 1:2 to 1:200, preferably in the range from 1:10 to 1:50, most preferably in the range 1:15 to 1:30.

In a typical procedure, a chamber containing a spray device is maintained at a temperature and pressure such that carbon dioxide (or other fluid) is supercritical. The temperature is controlled using an oven, and the pressure is controlled using a back pressure regulator at the chamber exit. A solution of paroxetine hydrochloride is prepared in a suitable solvent system and this solution and a supercritical fluid are separately metered to the spray device using high pressure pumps. Within, or close to the spray device, the supercritical fluid effectively removes the solvent from the paroxetine hydrochloride solution, giving a precipitate which is deposited in the collection chamber. When sufficient material has accumulated in the collection chamber the delivery of paroxetine hydrochloride solution is stopped. The paroxetine hydrochloride particles are rinsed with supercritical fluid to remove final traces of solvent and the apparatus is depressurised to harvest the product.

In an alternative method of operation the paroxetine hydrochloride is dissolved in the supercritical fluid or solvent-modified supercritical fluid using a saturator chamber. The resultant supercritical fluid solution is sprayed through a spray device into a second chamber at atmospheric or slightly above atmospheric pressure and particles of paroxetine hydrochloride are formed.

The temperature of the precipitation is generally from 15°C to 150°C, preferably from 45°C to 100°C, and the pressure is maintained in the range 25 to 300 bar, preferably from 100 to 200 bar.

When a crystalline product is desired, improved control of the precipitation process may be achieved by the addition of seeds. When the desired product is a hydrate such as paroxetine hydrochloride hemihydrate, an amount of water should be present in excess of the amount required according to theory.

The solid product of this invention may be formulated for therapy in the dosage forms described in EP-A-0223403 or WO96/24595. Free-flowing solids are advantageous for the preparation of solid formulations. Easily soluble solids are suitable for the preparation of solutions for parenteral use.

Therapeutic uses of the paroxetine product of this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the disorders".

Accordingly, the present invention also provides:

a pharmaceutical composition for treatment or prophylaxis of the disorders comprising solid paroxetine hydrochloride obtained by the process of this invention and a pharmaceutically acceptable carrier or a solution of the obtained solid paroxetine hydrochloride;

the use of solid paroxetine hydrochloride obtained by the process of this invention to manufacture a medicament in solid or liquid form for the treatment or prophylaxis of the disorders; and

a method of treating the disorders which comprises administering an effective or prophylactic amount of solid paroxetine hydrochloride obtained by the process of this invention, or a solution thereof, to a person suffering from one or more of the disorders.

The invention is illustrated by the following Examples:

Example 1

A particle collection chamber incorporating a spray device was maintained at a temperature of 45°C and a pressure of 95 bar. A 2% solution of paroxetine hydrochloride in a 50:10 acetone/propan-2-ol mixture containing 1.6% water was metered to the spray device at 0.40 ml/min. Supercritical carbon dioxide was also metered to the spray device at 9.0 ml/min. Paroxetine hydrochloride was deposited as low bulk density white powder.

Example 2

A particle collection chamber with a spray device was maintained at 50°C and 125 bar. A 2% solution of paroxetine hydrochloride in 110:10 acetone/propan-2-ol was metered to the spray device at 0.27 ml/min. Supercritical carbon dioxide was also metered to the spray device at 6.0 ml/min. Paroxetine hydrochloride was deposited as a dense white powder.

CLAIMS:

1. A process for isolating a solid form of paroxetine hydrochloride which comprises precipitating paroxetine hydrochloride from a solution thereof in a supercritical or near-critical fluid

2. A process according to claim 1 in which the solid form of paroxetine hydrochloride is crystalline.

3. A process according to claim 1 or 2 in which the supercritical fluid is carbon dioxide or ethane, n-propane, n-butane, or nitrogen oxide.

4. A process according to claim 1, 2 or 3 in which the paroxetine hydrochloride is first dissolved in an auxiliary solvent compatible with the supercritical fluid, and the solution brought into contact with the supercritical fluid to form a suitable solution for precipitation.

5. A process according to claim 4 in which the auxiliary solvent is ethanol, propan-2-ol, or isobutyl alcohol.

6. A process according to claim 4 or 5 in which an additional entraining solvent is employed to confer suitable properties on the auxiliary solvent.

7. A process according to claim 6 in which the supercritical fluid is carbon dioxide, the auxiliary solvent is propan-2-ol, and the entraining solvent is acetone.

8. A pharmaceutical composition for treatment or prophylaxis of the disorders comprising solid paroxetine hydrochloride obtained by the process of this invention and a pharmaceutically acceptable carrier or a solution of the obtained solid paroxetine hydrochloride.

9. The use of solid paroxetine hydrochloride obtained by the process of this invention to manufacture a medicament in solid or liquid form for the treatment or prophylaxis of the disorders.

10. A method of treating the disorders which comprises administering an effective or prophylactic amount of solid paroxetine hydrochloride obtained by the process of this invention, or a solution thereof, to a person suffering from one or more of the disorders.

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 99/03664

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 A61K31/4525

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 24595 A (SMITHKLINE BEECHAM PLC ;JACEWICZ VICTOR WITOLD (GB); WARD NEAL (GB) 15 August 1996 (1996-08-15) cited in the application page 6, line 5 - line 10; claims	1-10
A	WO 98 31365 A (WARD NEAL ;JACEWICZ VICTOR WITOLD (GB); SMITHKLINE BEECHAM PLC (GB) 23 July 1998 (1998-07-23)	1-10
A	EP 0 223 403 A (BEECHAM GROUP PLC) 27 May 1987 (1987-05-27) cited in the application examples	1,8-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2000	24/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

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INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 99/03664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 810 224 A (ASAHI GLASS CO LTD) 3 December 1997 (1997-12-03) cited in the application claim 1	1,8-10
A	WO 95 01221 A (UNIV BRADFORD ;HANNA MAZEN (GB); YORK PETER (GB)) 12 January 1995 (1995-01-12) abstract	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03664

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ›nal Application No
PCT/GB 99/03664

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